Remarks

All of the amendments and remarks set forth in the previous reply are incorporated herein by reference in their entirety.

In paragraph 14 of the outstanding Office Action, the Examiner has rejected claims 34 and 59 under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 4,725,585 to Wenge et al (Wenge). In paragraph 15, the Examiner has rejected claim 57 under 35 U.S.C. § 102(b) as anticipated by Noble et al (Noble). In paragraph 18, the Examiner has rejected claims 34-43 and 57-59 under 35 U.S.C. § 103(a) as obvious over Brand et al., Eur. J. Immunol. 1998. 28:1673-1680 (Brand). Applicants respectfully traverse these rejections.

In the previous reply, Applications amended the claims, without acquiescence in any rejection, to recite hyaluronic acid fragments that comprise from 2 to 12 building blocks, which are about 2000-5000 Da size. Applicants respectfully submit that none of the above references, either alone, or in any combination, teach or suggest the claimed invention. As objective evidence, Applicants submit herewith a Declaration of Dr. Jan Simon under 37 C.F.R. § 1.132 (declaration) as mentioned on page 6 of the previous reply.

Specifically, as mentioned on paragraph 4 of the declaration, Wenge teaches a method that uses hyaluronic acid of 750,000 Da. In addition, Noble teaches a method that uses hyaluronic acid of 200,000 Da, as mentioned in paragraph 5 of the declaration. However, the declaration clarifies that the molecular weight of the fragments of the instant invention, i.e., of 2-12 disaccharide length are much smaller, and their size is 2000-5000 Da size. Thus, Wenge and Noble fail to anticipate the claims of the instant invention since these references fail to teach hyaluronic acid fragments that comprising from 2 to 12 building blocks.

In addition, the declaration shows that high-molecular weight fragments such as those described by Wenge are ineffective to stimulate dendritic cell. In particular, human monocyte-derived dendritic cells were cultured for 48 hours in medium with 30

μg/ml of different fragment concentrations, all prepared from endotoxin-free, high molecular weight (500-100 kDa size) hyaluronic acid (HMW-HA). The HMW-HA was sonified to generate intermediate sized hyaluronic acid fragment of 300-60 kDa size (INT-HA). Finally, low molecular weight oligosaccharides were generated by enzymatic digestion and gel column separation (2-5 kDa) (sHA).

The effect of the fragments on phenotypical changes in dendritic cells are shown in the Figure, wherein the numbers behind the sHA indicate the number of disaccharide units (size) of the oligosaccharides (filled bars). Dendritic cells were then stained with monoclonal antibodies directed against surface markers.

The results are shown as mean fluorescence intensities (MFI). Importantly, only sHA, including those fragments of the instant invention, induce phenotypical changes in dendritic cells that can be correlated with dendritic cell maturation. The INT-HA and HMW-HA fragments, including those fragments disclosed by the applied references did not induce phenotypical changes in dendritic cells. *See* paragraphs 9 and 10 of the declaration.

Based on the foregoing, the dendritic cell maturation achieved using hyaluronic acid fragments that comprise from 2 to 12 building blocks is completely unexpected in view of Wenge and Brand, since these references are silent as to the unexpected results achieved using fragments that comprise from 2 to 12 building blocks. Therefore, these references fail to motivate one of ordinary skill to modify their disclosures to include hyaluronic acid fragments that comprise from 2 to 12 building blocks. Accordingly, Wenge and Brand fail to teach or suggest the instant invention.

Applicants submit that the Examiner must take the statements in the Declaration as objective evidence, not mere arguments, and cannot discount its contents. *See* M.P.E.P. § 716(c) (the Examiner is urged to consider the factual statements within the Declaration as objective evidence, which carry more weight than arguments alone).

In paragraphs 11 and 12 the declaration shows that Brand describes the role of extracellular matrix components of fibrinogen and type I and IV collagen, not hyaluronic

acid fragments. In contrast, the claims of the instant application recite hyaluronic acid fragments. Thus, Brand fails to teach or suggest the use of oligosaccahrides, much less hyaluronic acid fragments from 2 to 12 building blocks.

Brand also does not motivate one of ordinary skill to modify its disclosure to include the claimed hyaluronic acid fragments, since Brand does not teach or suggest the unexpected results on phenotypical changes in dendritic cells demonstrated by hyaluronic acid fragments that comprise from 2 to 12 building blocks, as instantly claimed.

Noble fails to remedy the deficiencies of Brand in teaching the instant invention since Noble describes a method that uses hyaluronic acid fragments of 200,000 Da size. By contrast, the claimed low-molecular weight oligosaccharides of 2-12 disaccharide length are of 2000-5000 Da size. Further, as shown in the attached declaration, intermediate sized fragments of 300,000 - 60,000 Da size, including fragment lengths reported by Noble are ineffective to stimulate dendritic cells. Accordingly, any combination of Brand and Noble fails to teach or suggest the instant invention. Accordingly, reconsideration and withdrawal of the rejection under § 103(a) are respectfully requested.

In view of the instant declaration and remarks, reconsideration of the application and allowance of all claims is requested. If there are any issues remaining that the Examiner believes could be resolved through either a Supplemental Response or an Examiner's Amendment, the Examiner is respectfully requested to contact the undersigned at the local exchange listed below.

Respectfully submitted,

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